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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/566,898	10/26/2006	Ellen Jessouroun	NIH275.001NP2	9576
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EXAMINER				
ARCHIE, NINA				
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/566,898

Applicant(s)

JESSOUROUN ET AL.

Examiner

Nina A. Archie

Art Unit

1645

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on 16 April 2008.
2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-14 is/are pending in the application.
4a) Of the above claim(s) _____ is/are withdrawn from consideration.
5) ☐ Claim(s) _____ is/are allowed.
6) ☒ Claim(s) 1-14 is/are rejected.
7) ☐ Claim(s) _____ is/are objected to.
8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SF/08)
Paper No(s)/Mail Date 4/16/2008
4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____

DETAILED ACTION

1. This Office is responsive to Applicant's amendment and response filed 4-16-08. Claims 1-14 are pending.

Information Disclosure Statement

2. The information disclosure statement filed on 4/16/2008 has been considered. An initialed copy is enclosed.

Claim Rejections Maintained - 35 USC § 103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

3. The rejection of claims 1-14 under 35 U.S.C. 103(a) as being unpatentable over Lees, A US Patent No. 5849301 Date December 15, 1998 in view of Penney et al US Patent No. 5773007 Date June 30, 1998, and Peetermans et al US Patent No. 6756040 Date 6/29/2004 US Filing Date May 23, 2002 is maintained for the reasons set for in the previous office action.

Applicant arguments:

To establish a prima facie case of obviousness, three basic criteria must be met: first, the prior art reference (or references when combined) must teach or suggest all the claim limitations; second, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; finally, there must be a reasonable expectation of success. See M.P.E.P. § 2143. Lees, Penney et al. and Peetermans et al. do not teach or suggest all of the limitations of pending Claim 1 and its corresponding dependent Claims 2-14, and thus a prima facie case of obviousness cannot be established. Moreover, Lees teaches away from the invention. The totality of the prior art must be considered, and proceeding contrary to accepted wisdom in the art is evidence of nonobviousness. In re Hedges, 783 F.2d 1038, 228 USPQ 685 (Fed. Cir. 1986). A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention. W.L. Gore & Associates, Inc. v. Garlock, Inc., 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), cert. denied, 469 U.S. 851 (1984).

Pending Claim 1 recites "[a] method for preparing a conjugate vaccine, the method comprising: reacting a polysaccharide with an oxidizing agent, whereby a solution of an aldehyde-activated polysaccharide is obtained; reacting a protein with hydrazine dichloride at an acidic pH, whereby a solution of a hydrazine-activated protein is obtained; reacting the aldehyde- activated polysaccharide with the hydrazine- activated protein at a pH of from about 5 to about 7 in the presence Of sodium cyanoborohydride, whereby a conjugate is obtained; and neutralizing unreacted aldehyde groups with adipic acid dihydrazide, whereby a conjugate vaccine capable of

stimulating an immune response is obtained" (emphasis added). In the Office Action it is asserted that Lees teaches the highlighted step. Applicants respectfully disagree.

In the Background of the Invention section of Lees, various techniques for reacting and modifying carbohydrates, such as polysaccharides, are discussed. These include utilizing aldehyde groups on the polysaccharide; however, Lees teaches away from such techniques due to the slowness and low yields of such methods:

Coupling of proteins can also be achieved through reductive amination, either using the aldehyde found on the reducing end of the polysaccharide or created by oxidation of the carbohydrate. Both of these approaches have intrinsic limitations and, thus, for high molecular weight polysaccharides, coupling through the reducing end is usually slow and inefficient and oxidation often results in cleavage of the polysaccharide chain or otherwise affects the antigen. (Lees, col. 3, lines 22-25).

Other carbohydrates have aldehyde groups at the terminal reducing end that can be exploited for derivatization and conjugation. It is also possible to create aldehyde groups with oxidizing reagents, e.g., sodium periodate. Aldehyde groups can be condensed with amino groups on protein or with a bifunctional linker reagent. This condensation reaction, especially with the terminal reducing end of a high molecular weight polysaccharide, however, often proceeds quite slowly and inefficiently. This is exacerbated when directly conjugating carbohydrate aldehydes to proteins. Thus, yields are often very low using this method. Moreover, sodium periodate may break up carbohydrates into smaller fragments and/or disrupt epitopes, which may be undesirable. (Lees, col. 3, lines 42-55).

Recognizing the disadvantages of these prior art methods, Lees notes that:

Most carbohydrates must be activated before conjugation, and cyanogen bromide is frequently the activating agent of choice To briefly summarize the CNBr-activation method, cyanogen bromide is reacted with the carbohydrate at a high pH, typically a pH of 10 to 12. At this high pH, cyanate esters are formed with the hydroxyl groups of the carbohydrate. These, in turn, are reacted with a bifunctional reagent, commonly a diamine or a dihydrazide. These derivatized carbohydrates may then be conjugated via the bifunctional group. In certain limited cases, the cyanate esters may also be directly

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reacted to protein. (Lees, col. 3, line 56 to col. 4, line 7).

However, this particular method utilizing cyanogen bromide suffers drawbacks too, as noted by Lees, including damage to the carbohydrate or protein components of the conjugate due to the high pH and instability of the cyanate ester at high pH, and difficulties in controlling the cyanogen bromide activation reaction. Lees also discusses modification of proteins by adipic dihydrazide in the context of the cyanogen bromide method, but again, teaches away from such techniques due to excessive crosslinking and polymerization:

Limited derivatization of the protein by addition of a limited number of spacer groups, such as hexane diamine or adipic dihydrazide, has also been proposed. These may then be added, for example, by the cyanogen bromide method. In this method, protein carboxyls are activated with carbodiimides and reacted with the amine or hydrazide. This method, however, produces extensive crosslinking of protein and polysaccharide and polymerization of the protein. (Lees, col. 5, lines 15-22).

Lees' solution to the drawbacks of the cyanogen bromide method and other prior art methods discussed is to activate the carbohydrate with 1-cyano-4(dimethylamino)-pyridinium tetrafluoroborate (CDAP) at a pH of 6 to 10. The resulting CDAP-activated carbohydrate is then either directly conjugated to the protein, or conjugated to, e.g., a protein that has been derivatized with a hydrazine.

Lees neither teaches nor suggests reacting an aldehyde-activated polysaccharide with a hydrazine-activated protein at a pH of from about 5 to about 7 in the presence of sodium cyanoborohydride, whereby a conjugate is obtained. To the contrary, Lees explicitly teaches away from conjugating an aldehyde-activated polysaccharide to a protein (see Lees at col. 3, lines 22-25 and lines 42-55). Lees also teaches that a high pH (10 to 12) is necessary for use in methods wherein cyanate ion (CN⁻) is generated (i.e., the cyanogen bromide activation method).

Applicants have discovered, despite teachings to the contrary in Lees and the other cited references and prior art, that aldehyde-activated polysaccharides can be employed as a reactant in a conjugation reaction to yield conjugate in high yield in a rapid reaction. Applicants have further discovered that it is not necessary to first activate

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a polysaccharide with CDAP in order to conduct a conjugation reaction at low pH, nor is it necessary to expose the polysaccharide to a high pH if cyanate generated is present. Applicants have surprisingly found that an aldehyde-activated polysaccharide can be conjugated to a protein in the presence of sodium cyanoborohydride - an inorganic cyanating agent that generates cyanate ions - at low pH (5 to 7) when the protein has first been activated with hydrazide. This particular reaction is neither taught nor suggested by Lees.

Neither Penney et al. nor Peetermans et al. include teachings overcoming the deficiencies of Lees. Penney et al. teaches conjugation of an oxidized polysaccharide fragment directly to tetanus toxoid monomer in the presence of sodium cyanoborohydride, but does not teach or suggest a hydrazide-modified protein. The only disclosure of Penney et al. regarding a hydrazide is a mention of the use of a symmetric linker such as adipic acid dihydrazide as described by Schneerson et al., J. Experimental Medicine, 152, 361-376 (1980). As noted in Applicants' application as filed, the Schneerson method is a cyanogen bromide conjugation method wherein the polysaccharide was subjected to a high pH of 10.5 (see Schneerson et al., page 363, paragraph entitled "HIB PS-Protein Conjugates"). Peetermans et al. includes similar disclosures as Penney et al., namely a description of cyanogen bromide coupling as described in Chu et al., Infect Immun. 1983 April; 40(1): 245-256. Again, the polysaccharide was subjected to a high pH of 10.5 (see Chu et al., page 247, first column, third full paragraph). Accordingly, the disclosures of Penney et al. and Peetermans et al. are therefore cumulative to the disclosures of Lees.

Because a method for preparing a conjugate vaccine comprising, inter alia, reacting an aldehyde-activated polysaccharide with a hydrazine-activated protein at a pH of from about 5 to about 7 in the presence of sodium cyanoborohydride, whereby a conjugate is obtained is neither taught nor suggested by Lees, Penney et al. and Peetermans et al., alone or in combination, and is, in fact, taught away from by Lees, a prima facie case of obviousness cannot be established. Applicants therefore respectfully request withdrawal of the rejection.

Examiner's Response to Applicant's Arguments:

Applicant's arguments have been fully considered but are not deemed to be persuasive. Examiner accepts amendments that have been made to claims (1 and 11). Examiner understands the recent decision by the Supreme Court in *KSR Int'l Co. v. Teleflex, Inc.*, No 04-1350 (U.S. Apr. 30, 2007). In response to applicant's arguments the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). This is why the references are combined under 35 U.S.C. § 103(a). Examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

Examiner states that Lee does not teach away from techniques. Examiner notes that column 3 is the background information not the invention of the prior art providing motivation to immunogenic constructs and how to maintain the integrity of the structure and preserve epitopes.

Therefore Lees A teaches a method for preparing a conjugate vaccine, the method comprising: reacting a polysaccharide with an oxidizing agent (sodium periodate), whereby a solution of an aldehyde-activated polysaccharide is obtained; reacting a protein with hydrazine at an acidic pH (see column 6 lines 65-67, column 7 lines 1-3, "reaction of hydrazides"), whereby a solution of a hydrazine-activated protein is obtained; whereby a conjugate is obtained; and neutralizing unreacted aldehyde groups with acidic acid dihydrazide, whereby a conjugate vaccine capable of stimulating an immune response is obtained, wherein the oxidizing agent comprises NaIO₄ (see column 5 lines 27-32), wherein the solution of the aldehyde-activated polysaccharide is buffer exchanged with a HEPES buffer, wherein the solution of the aldehyde-activated polysaccharide is buffer exchanged to a pH of from about 7 to about 8 (column 11 lines

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55-65), wherein the solution of the hydrazine-activated protein is buffer exchanged with a carbonate buffer (column 11 lines 55-65), wherein the solution of the hydrazine-activated protein is buffer exchanged to a pH of from about 10.0 to about 11.0, wherein a pH of the solution of the hydrazine-activated protein is raised to from about 7.0 to about 11 before the solution of the hydrazine-activated protein is buffer exchanged to a pH of from about 10.0 to about 11.0, whereby substantially all unreacted compounds and unconjugated polysaccharides are removed, yielding a purified conjugate vaccine, wherein the polysaccharide is selected from the group consisting of Meningococcal polysaccharides, Pneumococcus polysaccharides, Hemophilus influenzae type b polysaccharide, and group B Streptococcus polysaccharides, wherein the protein is selected from the group consisting of tetanus toxoid, diphtheria toxoid, and CRM197 (see column 9 lines 1-7), further comprising the step of adding saccharose as a stabilizer to the concentrated purified conjugate vaccine (see column 15), yielding a stabilized conjugate vaccine further comprising the step of concentrating the purified conjugate vaccine by tangential flow ultrafiltration (see column 11), yielding a concentrated purified conjugate vaccine, wherein the aldehyde-activated polysaccharide is reacted with the hydrazine-activated protein at a ratio of from about 1:1.6 to about 1:5 (see column 12 lines 50-57).

As to the limitation of claim 1 wherein the hydrazine-activated protein at a pH 5 to about 7. The prior does not teach the specific range of pH as claimed. The amount of a specific pH in a method is clearly a result effective parameter that a person of ordinary skill in the art would routinely optimize. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454,456, 105 USPQ 233, 235 (CCPA 1955). Thus, optimization of general conditions is a routine practice that would be obvious for a person of ordinary skill in the art to employ. It would have been customary for an artisan of ordinary skill to determine the optimal amount of each ingredient to add in order to best achieve the desired results. Thus, absent some demonstration of unexpected results from the claimed parameters, this optimization of ingredient amount would have been obvious at the time of applicant's invention.

Penney et al teach a method step of reacting the aldehyde-activated polysaccharide with the hydrazine- activated protein at a pH in the presence of sodium cyanoborohydride (see "Polysaccharide Conjugates")

Peetermans et al teach a method comprising the step of freeze drying the concentrated purified conjugate vaccine, yielding a dried conjugate vaccine (see claims and "Description").

As to claim 1, that recites "hydrazine dichloride". The reference teaches "hydrazine". Hydrazine dichloride is hydrazine in a salt form as evidenced A. E. Tutton Nature 1891 No. 1105 Vol. 43 pgs. 205-210) therefore Lees anticipates "hydrazine dichloride".

One would have motivated at the time the invention was made to incorporate a method step of reacting the aldehyde-activated polysaccharide with the hydrazine-activated protein at a pH in the presence of sodium cyanoborohydride as taught by Penney et al into the method as taught by Lees because both teach a method of preparing a conjugate vaccine. It would also have been prima facie obvious at the time the invention was made to incorporate a of freeze drying the concentrated purified conjugate vaccine, yielding a dried conjugate vaccine as taught by Peetermans et al into the method as taught by Lees because both teach a method of preparing a conjugate vaccine.

Therefore it remains obvious to combine them, even without an express statement of motivation. KSR forecloses the argument that a specific teaching, suggestion, or motivation is required to support a finding obviousness. See the recent Board Decision Ex parte Smith, --USPQ2d--, slip op. at 20, (Bd. Pat. App. & Interf. June 25, 2007 (citing KSR, 82 USPQ2d at 1396) available at <http://www.uspto.gov/web/offices/dcom/bpai/prec/fd071925.pdf>).

As outlined previously, the instant claims are drawn to a method for preparing a conjugate vaccine, the method comprising: reacting a polysaccharide with an oxidizing agent, whereby a solution of an aldehyde-activated polysaccharide is obtained; reacting a protein with hydrazine dichloride at an acidic pH, whereby a solution of a hydrazine-activated protein is obtained; reacting the aldehyde-activated polysaccharide

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with the hydrazine- activated protein at a pH of from about 5 to about 7 in the presence of sodium cyanoborohydride, whereby a conjugate is obtained; and neutralizing unreacted aldehyde groups with acidic acid dihydrazide, whereby a conjugate vaccine capable of stimulating an immune response is obtained.

Lees A teaches a method for preparing a conjugate vaccine, the method comprising: reacting a polysaccharide with an oxidizing agent (sodium periodate), whereby a solution of an aldehyde-activated polysaccharide is obtained; reacting a protein with hydrazine at an acidic pH (see column 6 lines 65-67, column 7 lines 1-3, "reaction of hydrazides"), whereby a solution of a hydrazine-activated protein is obtained; whereby a conjugate is obtained; and neutralizing unreacted aldehyde groups with acidic acid dihydrazide, whereby a conjugate vaccine capable of stimulating an immune response is obtained, wherein the oxidizing agent comprises NaIO_4 (see column 5 lines 27-32), wherein the solution of the aldehyde-activated polysaccharide is buffer exchanged with a HEPES buffer, wherein the solution of the aldehyde-activated polysaccharide is buffer exchanged to a pH of from about 7 to about 8 (column 11 lines 55-65), wherein the solution of the hydrazine-activated protein is buffer exchanged with a carbonate buffer (column 11 lines 55-65), wherein the solution of the hydrazine-activated protein is buffer exchanged to a pH of from about 10.0 to about 11.0, wherein a pH of the solution of the hydrazine-activated protein is raised to from about 7.0 to about 11 before the solution of the hydrazine-activated protein is buffer exchanged to a pH of from about 10.0 to about 11.0, whereby substantially all unreacted compounds and unconjugated polysaccharides are removed, yielding a purified conjugate vaccine, wherein the polysaccharide is selected from the group consisting of Meningococcal polysaccharides, Pneumococcus polysaccharides, Hemophilus influenzae type b polysaccharide, and group B Streptococcus polysaccharides, wherein the protein is selected from the group consisting of tetanus toxoid, diphtheria toxoid, and CRM197 (see column 9 lines 1-7), further comprising the step of adding saccharose as a stabilizer to the concentrated purified conjugate vaccine (see column 15), yielding a stabilized conjugate vaccine further comprising the step of concentrating the purified conjugate vaccine by tangential flow ultrafiltration (see column 11), yielding a

concentrated purified conjugate vaccine, wherein the aldehyde-activated polysaccharide is reacted with the hydrazine-activated protein at a ratio of from about 1:1.6 to about 1:5 (see column 12 lines 50-57).

Lees et al does not teach a method step of reacting the aldehyde-activated polysaccharide with the hydrazine- activated protein at a pH of from about 5 to about 7 in the presence of sodium cyanoborohydride, further comprising the step of freeze drying the concentrated purified conjugate vaccine, yielding a dried conjugate vaccine.

Penney et al teach a method step of reacting the aldehyde-activated polysaccharide with the hydrazine- activated protein at a pH in the presence of sodium cyanoborohydride (see "Polysaccharide Conjugates")

Peetermans et al teach a method comprising the step of freeze drying the concentrated purified conjugate vaccine, yielding a dried conjugate vaccine (see claims and "Description").

As to claim 1, that recites "hydrazine dichloride". The reference teaches "hydrazine". Hydrazine dichloride is hydrazine in a salt form as evidenced A. E. Tutton Nature 1891 No. 1105 Vol. 43 pgs. 205-210) therefore Lees anticipates "hydrazine dichloride".

It would have been prima facie obvious at the time the invention was made to incorporate a method step of reacting the aldehyde-activated polysaccharide with the hydrazine-activated protein at a pH in the presence of sodium cyanoborohydride as taught by Penney et al into the method as taught by Lees because both teach a method of preparing a conjugate vaccine. It would also have been prima facie obvious at the time the invention was made to incorporate a of freeze drying the concentrated purified conjugate vaccine, yielding a dried conjugate vaccine as taught by Peetermans et al into the method as taught by Lees because both teach a method of preparing a conjugate vaccine.

As to the limitation of claim 1 wherein the hydrazine-activated protein at a pH 5 to about 7. The prior does not does not teach the specific range of pH as claimed. The amount of a specific pH in a method is clearly a result effective parameter that a person of ordinary skill in the art would routinely optimize. "[W]here the general

conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454,456, 105 USPQ 233, 235 (CCPA 1955). Thus, optimization of general conditions is a routine practice that would be obvious for a person of ordinary skill in the art to employ. It would have been customary for an artisan of ordinary skill to determine the optimal amount of each ingredient to add in order to best achieve the desired results. Thus, absent some demonstration of unexpected results from the claimed parameters, this optimization of ingredient amount would have been obvious at the time of applicant's invention.

Status of the Claims

No claims are allowed.

Claims 1-14 are rejected.

9. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nina A. Archie whose telephone number is 571-272-9938. The examiner can normally be reached on Monday-Friday 8:30-5:00p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner supervisor, Shanon Foley can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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GAU 1645

REM 3B31

/Mark Navarro/

Primary Examiner, Art Unit 1645